REPORT

Edaravone in the Treatment of Amyotrophic Lateral Sclerosis: Efficacy and Access to Therapy—A Roundtable Discussion

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neuromuscular disease affecting approximately 5 out of every 100,000 individuals living in the United States. ALS is associated with 50% mortality within 30 months of initial symptom onset. The rarity of the disease, along with the significant inter- and intra-patient variability in clinical course and a lack of reliable biomarkers, have rendered the development of effective agents to treat ALS a challenge. Because oxidative stress is considered a contributing factor to ALS onset and progression, drugs that eliminate free radicals may protect motor neurons from damage potentially caused by free-radical and oxidative stress. Edaravone is an antioxidant free-radical scavenger approved by the FDA in 2017 for the treatment of ALS. A review of the edaravone clinical development program offers a clearer view of the clinical utility of this agent. Broader treatment success is also influenced by factors such as limited patient access and the restrictive payer environment. Cooperation within the healthcare community, among clinicians, patient advocacy groups, pharmaceutical companies, and managed care payers, must occur to advance ALS management and treatment and improve patient access. Moreover, collaborative discussions are useful in identifying potential solutions to problems currently surrounding patient access.

***Am J Manag Care*. 2018;24:S175-S186**

For author information and disclosures, see end of text.

Introduction

Objectives of the Roundtable Discussion

Mitsubishi Tanabe Pharma America and *The American Journal of Managed Care*® hosted a roundtable discussion to initiate a conversation among key health care stakeholders about the challenges and barriers to real-world management of amyotrophic lateral sclerosis (ALS), including patient access to treatment. Acknowledging their diverse perspectives, the participants highlighted the objectives, responsibilities, and challenges encountered in their respective roles, and discussed potential ways in which stakeholders can collaborate to improve appropriate patient access. As part of the conversation, participants discussed the recent edaravone clinical trials, interpretation of data, and how the data reflect and possibly inform the management of ALS in a broader, real-world setting.

Attendees

Roundtable participants represented key health care stakeholders important to the appropriate use of agents used to treat ALS and patient access. Key stakeholders included clinicians who specialize in ALS treatment, Dr Benjamin Brooks and Dr Jeremy Shefner; an advocate for patients with ALS, Ms Barbara Newhouse; a consultant to healthcare payers and health systems, Mr James Jorgenson; and 2 managed care payers, who did not participate in the development of this publication.

ALS Experts

Most ALS experts are neurologists and lead multidisciplinary teams, which collectively care for patients with ALS. They see, firsthand, the impact of this relentless and progressive disease, for which to date there is no cure. These expert clinicians are skilled at evaluating study outcomes and the clinical utility and relevance of these outcomes for their patients. As clinicians, they "have to look at individual patients and see where they might benefit from this treatment as we go forward," Dr Brooks observed. A common frustration of clinicians is the denial of coverage of ALS agents, such as edaravone, by payers when the clinician believes the patient may benefit from the agent. Dr Shefner stated that decisions regarding insurance coverage are the main barrier to patient access to edaravone.

ALS Advocates

Patient advocacy organizations, such as The ALS Association (ALSA), are often the public voice for patients and their families. They are particularly active and impactful in the rare diseases sphere; without their influence, such diseases would otherwise not get the attention or resources allocated to more prevalent diseases. ALSA's mission is "to discover treatments and a cure for ALS, and to serve, advocate for, and empower people affected by ALS to live their lives to the fullest." The association's primary focus is improving patients' quality of life and providing support that patients and their families need to cope with ALS. Knowing the extensive impact ALS has on a patient's quality of life, ALSA advocates zealously for unrestricted access to any therapy that may provide relief to a patient. "When you are facing a life-threatening disease…a 2.5-point difference [on the ALS Functional Rating Scale; ALSFRS] can make a huge difference in the life of somebody with ALS. It can make the difference between them perhaps living a bit longer and being able to be with their families," Ms Newhouse stressed. Appendix I provides a full discussion of the development of the ALSFRS, and studies examining the significance of point changes in its scoring metric.

Managed Care and Payers

Payers are tasked with the arduous responsibility of balancing economic and clinical dynamics for all disease states and afflictions, which impact their "covered lives population." The managed care participants explained the payer's perspective:

There is substantial pressure on payers to contain the cost of healthcare, and payers must make population-level decisions that are based upon population financial dynamics as much as clinical dynamics. As a rare disease with few treatment options, ALS is not frequently evaluated or discussed by those outside of the ALS community. Payers are not always familiar with scoring metrics used in clinical trials. A managed care participant elaborated, "When [payers] are dealing with these unfamiliar scales … they want to know if it relates to something that [patients] actually relate to and can notice a difference." Thus, a common challenge for payers is applying study data to a real-world population. As Mr Jorgenson noted, there is an unmet need for clinical models that can accurately extrapolate study data to a given population, providing payers with a more realistic expectation of a drug's impact on patients with ALS.

Background of ALS

ALS is a relentlessly progressive and fatal neuromuscular disease that is associated with 50% mortality within 30 months of initial symptom onset, and a lifespan of 3 to 5 years from the time of disease onset.[1,2] However, the disease course may vary depending on the patient and can be difficult to predict.[3] ALS is a rare disease that affects approximately 5 of every 100,000 individuals living in the United States,[4,5] totaling an estimated 30,000 individuals.[5,6]

ALS involves the progressive degeneration of nerve cells of the brain and spinal cord, leading to loss of voluntary muscle function.[7] It is characterized predominantly by upper motor neuron (UMN) and lower motor neuron (LMN) symptoms of degeneration.[1]

Patients with initial UMN symptoms typically present with difficulty walking due to muscle spasticity, while LMN symptoms initially manifest as muscle weakness, cramps, and muscle twitches.[1] Approximately 70% of patients with ALS present with limb-onset disease, 25% with bulbar-onset (eg, speech and swallowing difficulties), and 5% with initial truncal or respiratory involvement (eg, orthopnea, dyspnea), which will ultimately spread to other body regions.[1]

Diagnosis is complex and often delayed, coming 12 months on average after symptom onset.[8,9] This delay often precludes patients from benefiting from treatment that can be initiated in earlier stages of ALS, and it disqualifies patients from clinical trial consideration because, through no fault of their own, they exceeded the window of disease duration often required by study inclusion criteria.[9]

Due to the complexity of diagnosis, criteria have been developed to provide a uniform means of diagnosis.[11] The revised El-Escorial Criteria (rEEC), also known as Airlie House, are commonly used by clinicians and clinical investigators to categorize patients as having "definite," "probable," "possible," or "suspected" ALS.[11] Although the rEEC provide a level of certainty for diagnosis, they do not provide guidance regarding disease severity or progression.[3] Beyond the rEEC, there are no specific biomarkers of disease onset or progression that have been identified to date that clinicians, clinical investigators, or regulatory agencies can use to define the point a patient has reached in the continuum of their disease.[3]

Because no cure currently exists for ALS, the mainstay of treatment is symptom management and palliative care.[12] When the American Academy of Neurology (AAN) ALS guidelines were developed in 2009, the only disease-modifying agent approved for ALS treatment was riluzole.[13] Riluzole was approved in 1995 after clinical trials showed that it modestly slowed ALS progression. Twenty-two years passed before another agent was approved by the FDA for the treatment of ALS.[5,13,14]

The AAN's guidelines recommend multidisciplinary care, because study results have demonstrated that patients treated with multidisciplinary models have had longer survival, better quality of life, and greater access to therapies.[12] However, a study conducted by the AAN found that many evidence-based treatment recommendations were underutilized.[15] Consequently, an ALS quality measurement set was developed to provide expert guidance and best practices for managing ALS patient care (**Table 1**).[15] At the time those quality measures were published in 2014, riluzole was the only agent approved by the FDA for treatment of ALS; therefore, beyond recommending disease-modifying treatment, the measures focused mostly on patient referrals to multidisciplinary care clinics, appropriate screenings, and supportive symptom care.[13,15]

While multidisciplinary care has been shown to improve quality of life and overall survival in patients with ALS, these individuals will become unable to work as they increasingly lose functional ability to perform activities of daily living (ADL), such as driving.[1,16] Therefore, under the Social Security Administration's (SSA) Compassionate Allowance Program, patients with ALS can apply for disability benefits.[17] Patients will be covered starting 5 months after they have become disabled in accordance with the SSA definition of disability.[18] However, for patients with ALS, a 5-month waiting period may be difficult and burdensome to endure. Under Public Law 106-554, the 24-month waiting period for Medicare coverage for disabled individuals with ALS is waived.[19]

Given the evidence that former military personnel have an increased risk of ALS,[20] the Department of Veterans Affairs has recognized the increased prevalence of ALS in veterans and has classified ALS as a disease presumed to have been caused by military service. Veterans who are diagnosed with ALS and meet the criteria of continuously serving for 90 days or more will be qualified for "presumptive" disability benefits.[21]

Challenges and Advancements in ALS Study Design and Research

Historically, many challenges have precluded the development of efficient ALS clinical trials and effective ALS treatment.[22] From 1971 to 2013, 52 agents have been evaluated in ALS trials, with only 1 disease-modifying agent receiving FDA approval.[1,5,22,23]

The most significant challenges to developing effective ALS agents are the disease's rarity, the large inter- and intra-patient variability in clinical course, and the lack of reliable biomarkers and surrogate markers.[3,7,16,23] The heterogeneity of ALS' clinical course coupled with its low prevalence makes it difficult to obtain adequate sample sizes for clinical studies.[16] Evaluating a treatment agent's efficacy in slowing the progression of ALS is further complicated by its inherent heterogeneous and progressive nature and the lack of surrogate markers to accurately measure treatment response.[24] It is thus difficult to design a trial that can accurately correlate a patient's response to the study drug.

TABLE 1. American Academy of Neurology ALS Quality Measures[15]

Measure Title	Measure Description
ALS multidisciplinary care plan developed or updated	% of patients for whom a multidisciplinary care plan was developed, if not done previously, and the plan was updated at least once annually.
Disease-modifying pharmacotherapy for ALS discussed	% of patients with whom the clinician discussed disease-modifying pharmacotherapy (riluzole) to slow ALS disease progression at least once annually.
ALS cognitive and behavioral impairment screening	% of patients who are screened at least once annually for cognitive impairment and behavioral impairment.[a]
ALS symptomatic therapy treatment offered	% of patients offered treatment for pseudobulbar affect, sialorrhea, and ALS-related symptoms.
ALS respiratory insufficiency querying and referral for pulmonary function testing	% of patients who were queried about symptoms of respiratory insufficiency (awake or associated with sleep) and referred for pulmonary function testing at least every 3 months.[b]
ALS noninvasive ventilation treatment for respiratory insufficiency discussed	% of patients with respiratory insufficiency with whom the clinician discussed, at least once annually, treatment options for noninvasive respiratory support.[c]
ALS screening for dysphagia, weight loss, and impaired nutrition	% of patients who were screened at least every 3 months for dysphagia, weight loss, or impaired nutrition, and the result(s) of the screening(s) was documented in the medical record.
ALS nutritional support offered	% of patients with ALS and dysphagia, weight loss, or impaired nutrition who were offered, at least once annually, dietary or enteral nutrition support via percutaneous endoscopic gastrostomy or radiographic inserted gastrostomy.
ALS communication support referral	% of patients who are dysarthric who were offered a referral, at least once annually, to a speech-language pathologist for an augmentative/alternative communication evaluation.
ALS end-of-life planning assistance	% of patients who were offered, at least once annually, assistance in planning for end-of-life issues.[d]
ALS falls querying	% of visits for patients who were queried about falls within the past 12 months.

ALS indicates amyotrophic lateral sclerosis.
[a] Cognitive impairment screening such as frontotemporal dementia screening or ALS Cognitive Behavioral Screen; behavioral screening such as ALS Cognitive Behavioral Screen.
[b] Pulmonary function tests such as vital capacity, maximum inspiratory pressure, sniff nasal pressure, or peak cough expiratory flow.
[c] Noninvasive respiratory support such as noninvasive ventilation or assisted cough.
[d] Planning of end-of-life issues such as advance directives, invasive ventilation, hospice.
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ALS investigators have utilized several novel trial designs, including strategies to minimize sample size requirements and limit the study duration.[24] For example, use of homogenous subpopulations in clinical trials can increase statistical power and decrease a trial's duration.[3]

The revised ALS Functional Rating Scale (ALSFRS-R) was developed in 1999 to provide a more uniform method of measuring disease progression in clinical practice and measuring a study

drug's efficacy in clinical trials.[25] Because it is easily administered and reproducible, and correlates to other outcomes such as survival, the ALSFRS-R is well accepted by clinicians, patients, and regulatory authorities. This functional scale is based on 12 subjective assessments, each of a single ADL and which is rated on a 0- to 4-point scale. A score of 0 indicates inability to perform the ADL, and a 4 indicates normal ability to perform it. Thus, the total ALSFRS-R score ranges from 0 (maximum disability) to 48 (no functional disability).[25] **Table 2** provides the 12 assessments.[25] The results of a survey of clinicians of the Northeast ALS Consortium conducted by Castrillo-Viguera and colleagues suggested that a change of 25% or higher in the ALSFRS-R slope (total score divided by time) is clinically meaningful when considering the effectiveness of methods designed to slow the rate of progression.[26]

Studies have shown that the ALSFRS may have good internal consistency and retest reliability, and that both patients and physicians may notice differences between changes in ALSFRS scores.[27] In a trial that included 75 patients in a cross-sectional and 57 patients in a longitudinal study, the ALSFRS was tested for internal consistency, test/retest reliability, and responsiveness of the ALSFRS to change in functional status.[27] Results from the cross-sectional study showed that the ALSFRS demonstrated internal consistency and good reliability of both the individual terms and combined measures. In addition, the correlation between the ALSFRS items, limb-specific megascores, and results of pulmonary function tests were logically consistent with each other.[27] Results from the longitudinal study showed that patients and physicians could differentiate between changes in ALSFRS scores and functional status. Investigators found that both patients and physicians could differentiate a 2 or 3 point change compared with a 1 point or no change.[27]

Although the ALSFRS-R scoring metric provides advantages to ALS professionals involved in clinical practice and clinical trials, it is not without limitations. ALSFRS-R scoring is largely subjective and patient-specific.[9] It is a nominal scale, which has both intra- and inter-patient variability.[9]

Edaravone Clinical Development Program

Mitsubishi Tanabe Pharma Corporation designed the edaravone clinical development program with 2 primary goals: developing an effective treatment for ALS, and helping to create more efficient clinical trial designs to support future ALS research.[7] Lasting more than 13 years, the edaravone clinical development program involved a series of RCTs, extension trials, and post hoc analyses. Each subsequent trial incorporated key learnings and trial design strategies gleaned from the preceding ones. The following section provides highlights of the program. A more detailed exploration of the edaravone clinical trial program is found in Appendix II.

Edaravone, developed and studied in Japan for the treatment of ALS, is an antioxidant free-radical scavenger.[22,29] Because oxidative stress is considered a contributing factor to the onset and progression of ALS, drugs that eliminate free radicals may protect motor neurons from damage potentially caused by free-radical and oxidative stress.[28] Recognizing the unmet need for effective ALS treatment for patients in the United States, the FDA granted orphan drug status to edaravone in 2015, and subsequent gave edaravone its approval in 2017 with a broad indication: "for the treatment of amyotrophic lateral sclerosis (ALS)."[30,34] In its review of the edaravone clinical trials, the FDA noted that although there are reasons to believe that edaravone's efficacy may decrease as ALS progresses to advanced stages, this situation was not a valid reason to limit its use because the "variability of this disease precludes giving accurate information as to where the effect diminishes."[30]

The first phase 3 edaravone trial, MCI 186-16 (Study 16), was a multicenter, double-blind, placebo-controlled RCT that consisted of 2 study phases: a 12-week preobservational period and a 24-week treatment period.[28] Patients were randomized to receive daily edaravone 60 mg intravenous infusion or its matching placebo.[28] Patients aged 20 to 75 years were included if they met the following criteria: (1) diagnosis of "definite," "probable," or "laboratory-supported-probable" ALS; (2) % forced vital capacity (%FVC) ≥70%; (3) disease duration ≤3 years; and (4) decrease of 1 to 4 points in the total ALSFRS-R score during the 12-week preobservational period.[28] Patients enrolled were also required to have Japan ALS severity classification of 1 or 2, indicative of being able to live independently, with or without the capacity to perform work.[28] The primary end point was change in ALSFRS-R score.[28] A slower rate of disease progression, as represented by change in ALSFRS-R score, was seen in the edaravone group compared with the placebo group; however, the difference was not statistically significant.[28]

Study MCI 186-17 (Study 17) was an exploratory extension study of patients from Study 16. Patients who received edaravone in Study 16 were reassigned to receive edaravone or placebo for 24 weeks, while patients who received placebo in Study 16 were switched to edaravone. All patients were then offered open-label edaravone for the subsequent 12 weeks.[31]

A post hoc analysis of Study 16 was conducted to identify potential confounding variables that may have disproportionately biased the results of the study. One limitation identified was the large variability in clinical course of ALS among the patients enrolled, resulting in a wide range of changes in the ALSFRS-R score.[32] Study 16 investigators also found that 25% of patients in the edaravone group and 26% of patients in the placebo group had 0- or 1-point change in ALSFRS-R score over the 6 month study, indicating a more slowly progressing patient population than anticipated and/or powered for. Given the heterogeneity of the clinical course of ALS and the study's short (24-week) duration of treatment, the efficacy of edaravone, the analysis indicated, could have been masked by these confounding variables. Thus, the investigators

TABLE 2. Functional Assessments and Scoring on the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R)[25]

1. Speech

4 - Normal speech processes
3 - Detectable speech disturbance
2 - Intelligible with repeating
1 - Speech combined with nonvocal communication
0 - Loss of useful speech

2. Salivation

4 - Normal
3 - Slight but definite excess of saliva in mouth; may have nighttime drooling
2 - Moderately excessive saliva; may have minimal drooling
1 - Marked excess of saliva with some drooling
0 - Marked drooling; requires constant tissue or handkerchief

3. Swallowing

4 - Normal eating habits
3 - Early eating problems—occasional choking
2 - Dietary consistency changes
1 - Needs supplemental tube feeding
0 - NPO (*nil per os*; nothing by mouth) (exclusively parenteral or enteral feeding)

4. Handwriting

4 - Normal
3 - Slow or sloppy; all words are legible
2 - Not all words are legible
1 - Able to grip pen but unable to write
0 - Unable to grip pen

5a. Cutting food and handling utensils (patients without gastrostomy)

4 - Normal
3 - Somewhat slow and clumsy, but no help needed
2 - Can cut most foods, although clumsy and slow; some help needed
1 - Food must be cut by someone, but can still feed slowly
0 - Needs to be fed

5b. Cutting food and handling utensils (alternate scale for patients with gastrostomy)

4 - Normal
3 - Clumsy but able to perform all manipulations independently
2 - Some help needed with closures and fasteners
1 - Provides minimal assistance to caregiver
0 - Unable to perform any aspect of task

6. Dressing and hygiene

4 - Normal function
3 - Independent and complete self-care with effort or decreased efficiency
2 - Intermittent assistance or substitute methods
1 - Needs attendant for self-care
0 - Total dependence

7. Turning in bed and adjusting bed clothes

4 - Normal
3 - Somewhat slow and clumsy, but no help needed
2 - Can turn alone or adjust sheets, but with great difficulty
1 - Can initiate, but not turn or adjust sheets alone
0 - Helpless

8. Walking

4 - Normal
3 - Early ambulation difficulties
2 - Walks with assistance
1 - Nonambulatory functional movement
0 - No purposeful leg movement

9. Climbing stairs

4 - Normal
3 - Slow
2 - Mild unsteadiness or fatigue
1 - Needs assistance
0 - Cannot do

10. Dyspnea

4 - None
3 - Occurs when walking
2 - Occurs with 1 or more of the following: eating, bathing, dressing (activities of daily living)
1 - Occurs at rest, difficulty breathing when either sitting or lying
0 - Significant difficulty, considering using mechanical respiratory support

11. Orthopnea

4 - None
3 - Some difficulty sleeping at night due to shortness of breath. Does not routinely use more than 2 pillows
2 - Needs extra pillow in order to sleep (more than 2)
1 - Can only sleep sitting up
0 - Unable to sleep

12. Respiratory insufficiency

4 - None
3 - Intermittent use of bilevel positive airway pressure (BiPAP)
2 - Continuous use of BiPAP during the night
1 - Continuous use of BiPAP during the night and day
0 - Invasive mechanical ventilation by intubation or tracheostomy

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hypothesized that to properly detect treatment effects within the limited 24-week time-frame, a study population must have relatively good baseline function and relatively rapid progression.[32] Utilizing an enrichment strategy, the investigators identified subgroups whose changes in ALSFRS-R score could be expected to be more consistent.[32] Two subgroups were identified: Step 1, designated as Efficacy Expected Subpopulation (EESP), in which efficacy was expected from edaravone (%FVC ≥80% and ≥2 points for all items in the ALSFRS-R at baseline; and Step 2, designated as Efficacy Expected Subpopulation with definite or probable ALS and onset within 2 years (dpEESP2y), in which greater efficacy was expected. The dpEESP2y group was a subgroup of EESP consisting of patients who met the additional criterion of diagnosis of "definite" or "probable" ALS, and in which edaravone was started within 2 years of initial ALS symptom onset.[32]

The clinical investigators provided rationale for selecting these subgroups. Patients with advanced ALS disease may have a baseline score of ALSFRS-R 0 or 1 for any of the items; therefore, assessment of efficacy within a 24-week time frame would have been difficult in such a patient given that the patient lost all, or nearly all, ability to carry out that particular ADL prior to initiation of edaravone.[32] Patients with respiratory dysfunction may show rapid progression and thereby mask any effect of edaravone (ie, the floor effect on the ALSFRS-R).[32] Thus, the investigators determined that in order to accurately evaluate effects of edaravone within the short 24-week time frame, revised inclusion criteria were necessary. These revised inclusion criteria included: (1) diagnosis of "definite" or "probable" ALS; (2) FVC ≥80% (rather than ≥70%); (3) disease duration ≥2 years (rather than ≥3 years); and (4) a score of ≥2 on each item of the ALSFRS-R. The Japan ALS severity classification of 1 or 2 was preserved.[32] A post hoc subgroup analysis of Study 16 showed the decline in ALSFRS-R score was significantly less in the edaravone group for both the EESP (Step 1) and dpEESP2Y (Step 2) subgroups ($P = .0360$ and $P = .0270$, respectively).[32]

To confirm the findings of the post hoc analysis of Study 16, a randomized control trial, Study MCI 186-19 (Study 19), was developed, incorporating the revised inclusion criteria.[7] In this pivotal phase 3 trial, a significantly slower rate of progression was demonstrated in the edaravone group ($P = .0013$).[33] The mean change in ALSFRS-R score for the edaravone group from baseline to the end of the treatment period was −5.01 ± 0.64 compared with −7.50 ± 0.66 in the placebo group, producing a between-group difference of 2.49 ± 0.76 (95% CI, −0.99 to 3.98; $P = .0013$).[33] The loss of physical function was 33% less in patients treated with edaravone compared with those receiving placebo.[33] The score difference of 33% is considered clinically meaningful, because according to the study conducted by Castrillo-Viguera and colleagues, results suggested that a suppression of the ALSFRS-R score by 20% or more was considered to be clinically meaningful.[33] The results of Study 19 also showed that deterioration in quality of life was also significantly lower in the edaravone group compared with the placebo group ($P = .0309$).[33]

Based upon the pivotal findings of Study 19, the regulatory authorities in Japan, South Korea, and the United States approved edaravone for the broad indication of treatment of ALS.[34-36] Although the clinical trials were conducted entirely in Japan, the FDA found that the results were generalizable to the US population.[30]

The Current Payer Environment

Payers, both commercial and government, are key stakeholders in ALS management and can significantly affect patient access to ALS treatment. The challenges of the managed care and payer's environment were highlighted during the roundtable discussion. As the managed care participants described the difficulties of the payer environment, it became clear that a tension exists between the pressure for payers to stay within their budgets and the pressure to offer treatment access to patients who would benefit. The managed care participants explained that balancing the increasing pressure of controlling healthcare expenditures and patients' need for access in the context of limited clinical trial data results in payers often implementing initial policies with restrictive criteria. Thus, payers generally require data that conclusively demonstrate a drug's benefits in the given patient population in order to justify the cost.

This current payer environment has resulted in a reality in which there are major barriers to patient access to treatment for ALS, specifically managed care organization (MCO) policies that restrict access to treatment to a subpopulation of patients. Many MCO policies restrict coverage of edaravone to patients who meet criteria similar to Study 19's inclusion criteria and who can provide sufficient documentation of such.

Examples of common insurance policy criteria were presented at the roundtable for the participants to discuss (**Table 3**[1,3,37-41]). Mr Jorgenson, a consultant who works with healthcare payers and has previously worked in academic hospitals, opined that basing treatment access decisions on limited clinical trial data as opposed to the FDA label is a "slippery slope [...] Typically we see the approved FDA label as the basis for coverage determinations." The managed care participants explained the challenges payers experience in interpreting clinical trial data and expanding those data to a population that was not studied. These participants noted that, given the possibility that later stages of ALS are vastly different than earlier stages, it is difficult to extrapolate the clinical trial data to patients with advanced ALS. One managed care participant compared the situation with that of multiple sclerosis (MS), in which inflammation plays an important role in early disease; certain drugs effective in the early stage of MS become less effective in more advanced cases.

TABLE 3. Examples of Insurance Policy Criteria for Initial or Continued Access to Edaravone at the Time of the Roundtable Meeting[1,3,38-40,43]

Payer Criteria		Concerns With Criteria
Initial access		
Plan 1[a]	• Definite/probable ALS • %FVC ≥80% • ≥2 points on each ALSFRS-R item • ≤2 years of disease duration	• **≥2 Points on Each ALSFRS-R Item:** Patients may have limited functionality of any 1 of the ALSFRS-R items at time of diagnosis or shortly after diagnosis. For example, a patient who is able to grip a pen but unable to write would automatically disqualify them from coverage. • **FVC Criteria:** a significant portion of patients present with an FVC of less than 80% at time of diagnosis of ALS • **<3 on Japan ALS Severity Classification:** Japan ALS severity classification is not utilized in the United States; thus, clinicians would not be familiar with its application. • **≤2 Years of Disease Duration:** Rate of progression is highly variable intra- and inter-patient.There are also patients who have survived for more than a decade. Thus, it is possible that this criterion may bar access to a patient who has had ALS for >2 years but has progressed minimally and retains the same functionality as another patient who qualifies under the insurance policy.
Plan 2	• Definite/probable ALS • ≤2 years of disease duration • <3 on Japan ALS severity classification • ≥2 points on each ALSFRS-R item at time of therapy initiation	
Plan 3	• Initial approval for 6 months • Definite/probable ALS • ≥2 points on all ALSFRS-R items • %FVC ≥80% • ≤2 years of disease duration • Previous treatment and continued concomitant treatment with riluzole	
Plan 4	• Initial approval for 6 months • Definite or probable ALS • Independent living status[b] • %FVC ≥80% • ≤2 years of disease duration • ≥2 points on all ALSFRS-R items • Concomitant use of riluzole, at maximally indicated doses, unless contraindicated or AEs exist	
Plan 5	• Initial approval for 6 months • Definite/probable ALS • ≤2 years of disease duration • Can eat a meal, excrete, or move by oneself, and does not need assistance in everyday life • %FVC >80% • ≥2 points on all ALSFRS-R items	
Renewal of access		
Plan 3	• Continued therapy renewal every 6 months • Continues to meet all of initial review criteria • Documented evidence of efficacy or disease stability and/or improvement[c]	• ALS is a relentlessly progressive neurodegenerative disease. Damage to motor neurons is irreversible; thus, it would be impossible for patients to demonstrate "improvement." • The goal of treatment with ALS agents such as riluzole or edaravone is to decrease the rate of progression. • Rate of progression is highly variable inter- and intra-patient. A patient's progression without edaravone would be difficult to predict.
Plan 4	• Continued therapy for another 6 months • Responding positively to therapy (eg, no significant toxicity, no disease progression) • Continues to meet initial criteria	
Plan 5	• Reauthorization for another 6 months • Continued compliance with initial access criteria • Chart notes show improving signs and symptoms of disease • Documented ALSFRS-R score improvement	

[a] The criteria listed in Table 3 were in place at the time of the roundtable discussion. The criteria have subsequently been modified; %FVC of 80% or more is no longer required for initial authorization.
[b] A patient who can eat a meal, excrete, or move by oneself, and does not need assistance in everyday life.
[c] Does not have disability of independent ambulation, loss of upper-limb function, tracheotomy, use of a respirator, use of tube feeding, or loss of useful speech.
AE indicates adverse event; ALS, amyotrophic lateral sclerosis; ALSFRS-R, Revised ALS Functional Rating Scale; FVC, forced vital capacity.

Another managed care participant sought to provide a larger context for issues relating to access to treatment by noting that health plans experience ongoing pressures from pharmaceutical manufacturers who want to establish their products within formularies. Payers must remain unbiased in their evaluation of a drug's value proposition for their covered lives population. The managed care participant suggested that collaboration between payers and pharmaceutical companies may help to increase access.

Among the more notable restrictive policy criteria presented at the roundtable were policies' requirements for continued coverage of edaravone. It was speculated that the payers may have incorporated stringent criteria based on concerns about lack of oversight

after access is granted, in the circumstance where a patient does not respond but does, nevertheless, continue on edaravone. For example, a requirement that a patient shows documented efficacy of disease stability or improvement can demonstrate that they are positively responding, have no disease progression, or have an improved ALSFRS-R score.[39,41] Edaravone treatment is not intended to be a cure, but rather a treatment to slow progression of functional decline.[28] Considering that ALS is a "relentlessly progressive" disease, the notion that "disease stability or improvement" is required to support continued treatment is almost, by definition, a guarantee of denial of coverage. Dr Brooks shared from his own experience that he witnessed 2 of 21 patients showing improvement or stabilization by cycle 6. As this is an unusual response rate, Dr Brooks speculated that edaravone could lead to favorable outcomes and suggested that patients on edaravone should continue therapy.

The ALS experts and ALS advocates at the roundtable voiced their concerns that the limitations appear arbitrary and that they inappropriately limit patient access. Dr Shefner noted that "requiring ALS patients to either show no progression or actively improve with time is inconsistent with the way the disease progresses or with the current understanding of the level of efficacy that has been demonstrated with edaravone." A managed care participant agreed with Dr Brooks that the inconsistent policy criteria may have been due to lack of understanding of the disease. There was consensus among the roundtable participants that ALS educational campaigns for payers would be beneficial.

Since the roundtable meeting, several managed care payers have revised their criteria for coverage of edaravone to eliminate some of the requirements. For example, Plan 1 (Table 3) no longer requires FVC of 80% or more for initial authorization.[37] Plan 5 no longer requires disease duration of 2 years or less or FVC of 80% or more for initial reauthorization, and it modified the ALSFRS-R score requirement to a total of 20 points or more (as opposed to requiring 2 points or more on each of the 12 ALSFRS-R items).[42] Revisions of Plan 5 also extended coverage from 6 months to 12 months and removed reauthorization requirements of documented ALSFRS-R score improvement and documented evidence of improving signs and symptoms of ALS.[42]

Interpretation of the Edaravone Clinical Development Program

Interpretation of Inclusion Criteria of Study 19

The source of the highly debated issue of patient access to edaravone is the inclusion criteria of Study 19. There is a lack of consensus in the healthcare industry regarding interpretation of the restrictions on the inclusion criteria restrictions and the real-world application. The roundtable participants grappled with the question of whether using the inclusion criteria to define insurance policies inappropriately limits patient access.

Dr Shefner explained the utility in the enrichment strategy of Study 19: "Subgroup enrichment is potentially valuable in 2 circumstances. First, if the disease in question may be due to differing pathophysiological pathways, isolating patients by pathway may improve the ability to detect an effect of an agent intended to modify that pathway. Second, diseases with heterogeneity of progression rate will require large sample sizes in order to see a biologic effect superimposed on this level of heterogeneity. Selecting subjects with relatively uniform progression rates will allow a therapeutic effect to be detected with a smaller sample size. This was the strategy employed in the second phase 3 study of edaravone." Of note, given the ethical considerations of keeping patients with ALS on placebo long-term, the edaravone investigators determined that 24 weeks (6 months) of treatment was an ethically acceptable study duration of treatment. The inherent challenge of a short study duration is its inability to demonstrate long-term effects of the study drug. Thus, the edaravone investigators sought to design inclusion criteria to identify patients with an ALS clinical course that would more accurately demonstrate edaravone's efficacy within the 6-month time frame.[32]

> "The clinical trial criteria employed in study 19 were chosen so that a signal could be detected with a modest sample size and study duration; such design considerations should not serve as the basis for insurance approvals."
>
> – Jeremy M. Shefner, MD, PhD

Dr Brooks provided an example, from his practice, of a patient who would likely have benefited from edaravone, but whose respiratory scores excluded her from treatment coverage. He emphasized the importance of patients being considered on an individual basis for potential benefit with edaravone treatment. Restricting the inclusion criteria, he said, "does not mean that other patients [not meeting the criteria] may not have that treatment effect. It is just that within the 6-month period of time that treatment effect was identified in the clinical trial that was ethically accepted by the [Japanese] Pharmaceuticals and Medical Device Agency and by the Japanese clinical investigators."

Dr Shefner highlighted the potential consequence on future research of inappropriately limiting patient access based on clinical trial criteria. He explained that "a good clinical trial will evaluate efficacy using the absolute minimum number of subjects, both because this strategy limits the drug exposure and subsequently the undetermined adverse events to the fewest number of patients, and because clinical trials in rare diseases often enroll slowly or incompletely. Decisions made to achieve this goal do not have implications regarding patients who are likely to benefit from a

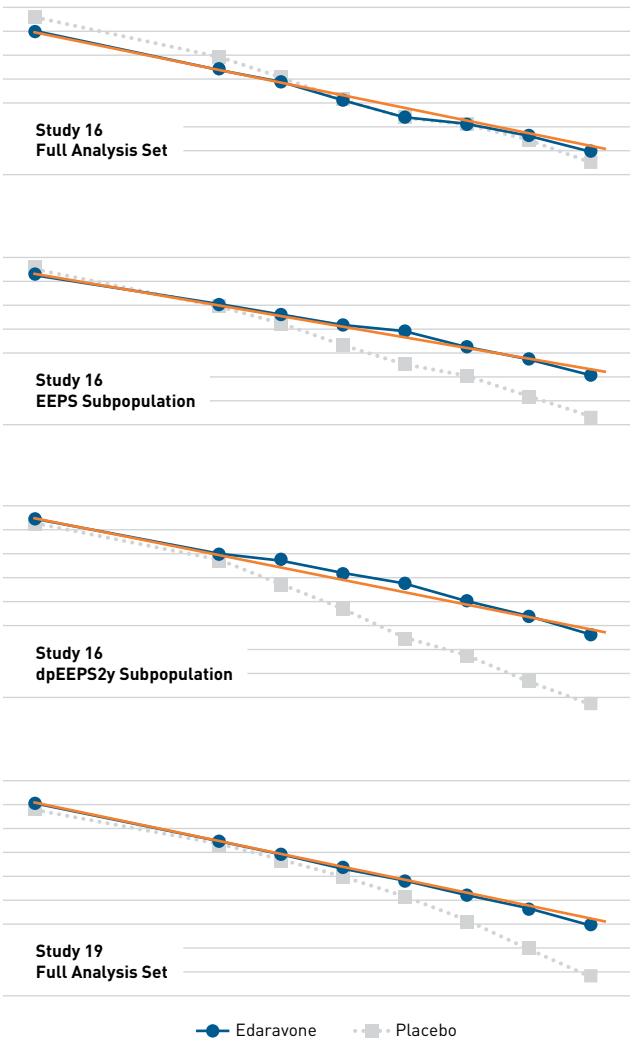
drug once it is approved. To the extent that insurance companies use such clinical trial criteria to make decisions about access, trials will become less efficient both with respect to duration and numbers of patients required." Dr Shefner pointed out that the Study 16 results showed trends toward benefit not only in the patients similar to those in Study 19, but in other subgroups as well (**Figure 1**).[31,33,50] He added that while there were smaller effect sizes in patients who progressed more slowly, the point estimates of effect, if accurate, would predict a significant disparity between treated versus untreated patients over 1, 2, or 3 years. However, a study powered to detect such differences would require a much larger sample size and longer duration.

Study 19 Patient Population Versus Real-World Patients with ALS

Diagnosis of ALS is often delayed, with an estimated onset of approximately 12 months after onset of initial symptoms,[5] which may lead to delays in starting appropriate pharmacologic therapy because the disease has already progressed.[1] Many healthcare plans require patients to have a minimum 2-point score on each of the 12 ALSFRS-R items (see Table 3); thus, limited functionality of any one of those assessment criteria (eg, inability to grip a pen, or inability to climb stairs) would result in denial of coverage.[25] Also, a subset of patients initially presents with respiratory symptoms,[1] but some healthcare plans additionally require a baseline FVC of 80% or more,[39,41] when FVC of 80% is considered almost normal respiratory function.[43] Therefore, patients who initially present with respiratory symptoms would be excluded from edaravone coverage under many healthcare plans even if they would possibly otherwise benefit. At many centers, respiratory compromise is advanced more than motor response and these patients may be able to benefit in terms of the motor effects of edaravone while respiratory function is supported by specific devices. The implementation of criteria for insurance coverage that mimics the inclusion criteria of Study 19 potentially eliminates a substantial portion of the real-world ALS patient population.

The FDA accepted the foreign clinical trial data, finding that ethnicity factors would not significantly impact a patient's response to edaravone. In the report released by the FDA Center for Drug Evaluation and Research giving its clinical review of edaravone, the agency found that "the summary of ethnic bridging provides sufficient support use of these data based upon the principles outlined [by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ICH] in the ICH Harmonised Tripartite Guideline Ethnic Factors in the Acceptability of Foreign Clinical Data E5 (R1) and the FDA's Guidance for Industry E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data."[30] Furthermore, as mentioned above, the FDA found a lack of evidence to warrant limiting edaravone's utility in advanced stages of ALS.[30]

FIGURE 1. Rate of Decline in ALSFRS-R Scores in Study 16 (FAS and EEPS and dpEEPS2y subpopulations) and Study 19 (FAS)[31,33,50]



ALSFRS-R indicates Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; dpEESP2y, Efficacy Expected Subpopulation with definite or probable ALS and onset within 2 years; EESP, Efficacy Expected Subpopulation; FAS, full analysis set.

Application of Findings from Edaravone Clinical Trials to Real-World ALS Management

The Importance of a 2.5-Point Difference

A key issue discussed by the roundtable participants was the difficulty experienced by those who are not ALS experts in understanding the clinical impact of changes in ALSFRS-R scores. The question of how to interpret changes in ALSFRS-R scores is another highly debated issue: What constitutes a meaningful change? How much of a difference does 1 or 2 points make in the life of a patient? The questions and scoring employed in the ALSFRS-R are shown in Table 2.[25]

In Study 19, the changes in ALSFRS-R scores seen in the edaravone group and placebo group were −5.01 and −7.50, respectively. The between-group difference in change in ALSFRS-R score was 2.49 points, a statistically significant difference ($P = .001$).[33] A debate on the clinical impact of a 2.5-point difference arose among the roundtable participants.

> Given that the ALSFRS-R amalgamates a broad spectrum of patient function, there is no direct way to determine how a patient may perceive a 2.5-point treatment effect. I believe it is more meaningful to evaluate the extent to which a patient's disease course has been impacted. A 33% slowing of disease progression over 6 months, as was noted in study 19, would be interpreted by both patients and physicians as being clinically meaningful. This is consistent with the results of a survey of ALS clinicians which noted that, while a change in progression rate of 10% or less was not regarded as clinically important, changes in progression rate of 25% or more were felt to be clinically meaningful.
>
> – Jeremy M. Shefner, MD, PhD

Ms Newhouse, a prominent advocate with strong relationships to patients with ALS, commented on how significant a seemingly minor change in ALSFRS-R score can be for a patient. She explained that patients with a life-threatening disease such as ALS may significantly benefit from a change of 2.5 points and have more valuable time with their families. The clinicians at the roundtable discussion noted that the degree of impact on a patient's quality of life is highly variable and patient-specific, because each patient may value functional domains differently. The significance of a change in ALSFRS-R also varies based on the specific ALSFRS-R item.

As noted by a managed care participant, payers are often not equipped to understand the clinical impact of scoring metrics, such as ALSFRS-R scores. He asked, "Is 2.5 points on a 48-point scale enough?" In addition, he also noted that 2 patients, side by side, might each experience a 2.5-point change in entirely different ways. He suggested addressing the "2.5-point problem" by performing a sensitivity analysis that would show the differences in implication of change across the patient population. What payers want to see, he explained, particularly when it comes to a scale with which they are not familiar, is how it relates to human experience and whether and why differences are noticeable. Payers need a way of understanding why a small point difference, even as low as 1 point when it comes to climbing stairs, may be significant, while other equivalent point changes are less so.

Addressing the issue of whether useful data could be acquired by following patients on and off edaravone in the clinic, Dr Shefner emphasized that the trajectory of decline in ALS has varied significantly across ALS studies. Although it is often stated that patients decline on average about 1 point per month, ALS trial data from the past 10 years have shown rates of progression over 6-12 months of 0.7 to 1.4 points per month, depending on the country, inclusion criteria, and other unknown factors. Thus, following a small number of patients in a single, or even multiple, clinics is not likely to add or subtract to the body of evidence supporting the use of edaravone.

The Relative Value of End Points: Survival Versus ALSFRS-R Versus Quality of Life

Although survival has been previously employed as a primary outcome measure in ALS trials, Dr Shefner contended that survival should not be considered as the only approvable endpoint in ALS trials. Survival trials require large numbers of patients studied for long periods; the original studies of riluzole in ALS involved more than 900 patients treated for 18 months, and the more recent study of dexpramipexole in ALS also enrolled more than 900 patients in order to effectively evaluate a survival benefit. Fortunately, the current therapeutic landscape is such that more trials are actively enrolling at any given time, so that the ability to enroll trials of this magnitude is reduced. Functional preservation is also clinically meaningful, and can be evaluated more efficiently. This is the case for Study 19, which was powered to a functionally important outcome but was not designed to detect a survival difference. In fact, the short trial duration and the inclusion of patients with early disease both acted to reduce the chance of death during the study. However, multiple studies have demonstrated that rate of progression as defined by decline in ALSFRS-R strongly correlates with long term survival.

A managed care participant agreed that demonstration of improvement or of prevention of deterioration in quality of life—something that "made a difference for the patient"—should justify coverage: "The point of medicine … is not just to extend life, but also improve the quality of the life that we're trying to extend." However, he noted that payers may not fully understand what an objective scoring metric translates to in the real world: "You have to be able to relate it to something that [payers] can put into perspective. We need to be able to describe what the 2.5 [-point ALSFRS-R score change] means."

Dr Brooks pointed out that in Study 19, there was a 1 in 8 chance of a patient experiencing no progression while taking edaravone results that, in terms of number needed to treat, were impressive. "The question is," he said, "how long will that treatment effect last? In the extension study, there's a suggestion that the patients who started this treatment early continued to have a better effect than those patients who began the treatment 6 months later. So I think these are strong clinical points that have to be put on the table

with respect to the decision making of whether we would give this medicine to people more broadly."

Previous studies, Dr Brooks stated, have compared the ALSFRS-R with other measures, including assessment of patient self-report and of Global Clinical Impression. "In the earlier papers, it was identified that the physicians and patients could identify a change in their disease status by Global Clinical Impression that was comparable with a 2.5 to 3.0 change on the ALS functional rating scale," he noted. "So from that point of view, I think the literature is quite clear that there is an important change that the patients can perceive if they have that kind of change." [27]

> "There's a 1 in 8 chance of having no progression or improvement, and that number-to-treat is quite impressive to me."
>
> – Benjamin Rix Brooks, MD

Collaborative Opportunities to Improve Patient Access to ALS Treatment

A myriad of passionate opinions from the different ALS healthcare stakeholders emerged during the roundtable discussion. However, all participants agreed that cooperation within the healthcare community, among clinicians, patient advocacy groups, pharmaceutical companies, and managed care payers, must occur to advance ALS management and treatment and improve patient access.

In wrapping up the discussion, the participants collaborated to develop potential ways the healthcare community could move forward with patient access and ALS management. To help payers justify expanded access, Dr Jorgenson proposed a pharmacoeconomic analysis—such as a cost utility analysis where costs are valued in monetary units and outcomes are valued in quality-adjusted life-years. Thinking about edaravone, it would appear to be a more effective but expensive treatment option where clinical effectiveness is gained at an increased cost. Payers must evaluate the whether the increased benefit in efficacy justifies the increased cost. Incremental cost effectiveness analysis can be used to determine the additional cost and effectiveness gained when one treatment such as edaravone is compared with the next best treatment alternative. Therefore, instead of comparing the average cost effectiveness ratios of each treatment alternative, the additional cost that edaravone treatment imposes over another treatment can be compared with the additional benefit it provides. However, he also noted that, while desirable, a pharmacoeconomic analysis would be hard to achieve with 6-month data.

The participants suggested educational initiatives. "I think we need an educational campaign for the insurance companies and the payers about ALS," said Dr Brooks. He stressed the importance of an educational approach that included models of how change in ALS is measured using the ALSFRS-R, and what these changes signify from a clinical perspective. Dr Brooks added that it was important to emphasize the success of the edaravone clinical trials in demonstrating the drug's contribution to improvement in measures of quality of life. The roundtable participants were in general agreement that education about ALS and its appropriate treatment, and how changes in disease measurement should be interpreted, are high priorities.

A managed care participant noted that educational campaigns can help payers define more efficient criteria, which would be a positive change, because inconsistent coverage criteria usually result in unwarranted denials that will be overturned upon appeal. Implementing more efficient criteria would help reduce administrative costs associated with processing those appeals.

Ms Newhouse believed that a crucial goal of such an educational campaign should be "helping people understand [what happens when the] FDA makes an approval—what that really means, and that there's not an entitlement that goes along with that." Specifically, she added, "a better job [needs to be done] of helping [payers] understand what an FDA approval means when it comes to the category of rare diseases."

Participants discussed the utility of clinical models, as well. Dr Jorgenson proposed the development of a clinical model predicting outcomes in an expanded-access patient population that would allow payers to see what they might expect. "Would it be achievable," he asked, "to build an accurate clinical model of what this might look like if I expand a patient population? That if I expand a patient population to include X, what might my model look like? [If it would,] then you can start to fit outcomes to the model, to give payers at least a more realistic expectation of what the impact of this might actually be." A managed care participant agreed, stating that a clinical model that could show what treatment effects may be expected in various subpopulations (eg, patients with lower baseline %FVC) would be useful to payers in developing more efficient criteria.

Overall, this diverse group of stakeholders in ALS patient care shared their expertise, rationales, and situational environmental considerations that ultimately drive their decisions and recommendations. Although their perspectives varied considerably, the participants agreed that collaborative discussions, such as those that occurred during this lively roundtable meeting, are useful in identifying potential solutions to problems currently surrounding patient access. ■

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Funding source: This supplement was funded by Mitsubishi Tanabe Pharma America, Inc.

Author disclosures: Dr Brooks is employed by the Carolinas Healthcare System Neurosciences Institute and serves on an Advisory Board for Mitsubishi Tanabe Pharma America; Dr Agnese is an employee of Mitsubishi Tanabe Pharma America; Ms Newhouse is a former employee of the ALS Association; Dr Shefner is employed by the Barrow Neurological Institute and serves on

an Advisory Board for Mitsubishi Tanabe Pharma America; Mr Jorgenson discloses participation as a compensated Advisory Board member for Mitsubishi Tanabe Pharma America.

Authorship information: Acquisition of data (BRB, JMS, WBA), administrative, technical, or logistic support (BRB); analysis and interpretation of data (BJN, BRB, JMS, WBA); concept and design (BRB, JAJ, WBA); critical revision of the manuscript for important intellectual content (BJN, BRB, JAJ, JMS, WBA); drafting of the manuscript (BRB, JAJ); supervision (WBA); provision of study materials or patients (BJN, BRB).

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